PAEDIATRIC RETINOBLASTOMA PRESENTATION IN A REGIONAL CANCER CENTRE IN PAKISTAN

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Abstract
Purpose: Retinoblastoma (RB) is a common paediatric intra-ocular tumour. In the developed world retinoblastoma accounts for <5% of all paediatric cancers. In the developing world retinoblastoma may comprise of about 10-15% of all diagnosed paediatric cancers according to hospital-based retrospective study in India.

Methods: Medical records for all diagnoses of retinoblastoma at our regional cancer centre were retrospectively reviewed from January 2005 to September 2015 after IRB approval.

Results: A total of 258 (100%) patient charts were reviewed. More male n=163 (63.2%) patients were seen than females n=95 (36.8%). Most patients were diagnosed before the age of 5 years. Positive family history was seen in 20 (7.8%) patients. Total number of bilateral disease was seen in 75 (29.1%) patients and 183 (70.9%) had unilateral diagnoses. Median age at presentation was 24 months for bilateral and 36 months for unilateral disease.

Conclusions: The median age at presentation shows significant delay in the establishment of diagnosis for both unilateral and bilateral RB. Compared to western data there was a higher number of male patients seen. Financial constraints, access to primary healthcare, lack of trained personnel and cultural practices are likely factors leading to delayed presentation and advanced disease state.

Keywords: Retinoblastoma, Ocular tumours, Leukocoria

Introduction:
Retinoblastoma (RB) is the most common intraocular tumour of childhood. It is associated with the retinoblastoma (RB1) gene mutation. When congenital it is present at birth and clinically picked up either during well-child checks or at an early age by parents. In cases where the disease is sporadic or non-hereditary it presents in a single eye later in life between 3 to 5 years of age. Two-thirds of all cases of retinoblastoma are diagnosed before the age of 2 years while 95% of cases are diagnosed before 5 years of age [1].

Incidence of retinoblastoma is considered to be constant around the world at one case per 15000–20000 live births, which corresponds to about 9000 new cases every year [2, 3]. Management of RB has improved over the years. Today in the developed world the early presentation of disease, access to care and advancement in therapy has led to a survival rate of more than 90% [4,5]. In developing countries these rates are lower secondary to different reasons and an important one being access to healthcare resulting in advanced disease at the time of presentation to the oncology service [6,7].

In the 1950's, the Reese-Ellsworth classification system was developed to predict the prognosis after treatment with radiation. Now clinicians are using the International Classification of Retinoblastoma (ICRB) to better predict outcomes of intraocular retinoblastoma without the need for external-beam radiation. The ICRB grading is as follows:

Group A: Small intraretinal tumors (< 3mm) away from foveola and disc.
Group B: Tumours > 3mm, macular or juxtapapillary location, or with subretinal fluid.
Group C: Tumour with focal subretinal or vitreous seeding within 3mm of tumour.
Group D: Tumour with diffuse subretinal or vitreous seeding > 3mm from tumour.
Group E: Extensive retinoblastoma occupying >50% of the globe with or without neovascular glaucoma, haemorrhage, extension of tumour to optic nerve or anterior chamber.

Disease presentation is varied and can include leukocoria, strabismus, proptosis, redness and so on. These symptoms can overlap with other ophthalmologic conditions. This can delay diagnosis by primary healthcare providers in developing countries not familiar with RB, a rare but common cancer in the eyes of young children. The aim of this study is to present our institutional experience of treatment and outcome in children with retinoblastoma seen at a large freestanding cancer hospital in Lahore, Pakistan.

Methods
We conducted a retrospective chart review of all patients diagnosed with retinoblastoma at a large regional cancer centre in Pakistan between January 2005 and September 2015. These patients were accepted into the system after a detailed history and exam. Studies done prior to starting treatment included ocular ultrasonography, examination under anaesthesia (EUA), computed tomography (CT) or a magnetic resonance imaging (MRI), bilateral bone marrow biopsy, lumbar puncture, audiometry and creatinine clearance. The data collection for this analysis included age at presentation, sex, family history of RB, clinical presentation, treatment administered, treatment compliance and outcome duration of survival.

Results
A total of 258 (100%) patients were treated during the study period. Out of these 163 (63.2%) were boys and 95 (36.8%) girls (Table 1). Chart review showed 183 (70.9%) patients had unilateral disease while 75 (29.1%) had bilateral disease. The median age of diagnosis for bilateral disease was 24 months (range, 2-96 months) and 36 months (range, 1-132 months) for unilateral disease. More than 50% of the patients were older than 24 months and the oldest age at presentation was 11 years.

There were 20 (7.8%) families who reported a positive family history for RB. Ten (50%) of these had unilateral disease and 10 (50%) had bilateral disease. The most common presenting symptoms were leukocoria n=145 (56.2%) and proptosis n=49 (18.9%). Chart review showed that 108 (41.8%) patients were lost to follow-up, 47 (18.2%) died and 103 (39.9%) were alive at the last follow-up at 2-years. 196 (75.9%) patients were treated surgically with an enucleation or exenteration whereas the rest of the 62 (24%) were those that were managed with chemotherapy without surgical intervention at our institution. Specimens for 163 (63.2%) patients were available for pathological review.

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>Numbers (%)</th>
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</thead>
<tbody>
<tr>
<td>1) Leukocoria</td>
<td>146 (56.6)</td>
</tr>
<tr>
<td>2) Proptosis</td>
<td>49 (19)</td>
</tr>
<tr>
<td>3) Extra-ocular mass</td>
<td>27 (10.5)</td>
</tr>
<tr>
<td>4) Vision loss</td>
<td>14 (5.4)</td>
</tr>
<tr>
<td>5) Strabismus</td>
<td>12 (4.7)</td>
</tr>
<tr>
<td>6) Others</td>
<td>10 (3.9)</td>
</tr>
</tbody>
</table>

M:F ratio 1.7:1

Our patients received chemotherapy consisting mainly of carboplatin, vincristine, etoposide, cyclophosphamide and doxorubicin in addition to enucleation. No facilities for cryotherapy, brachytherapy, intra-vitreal or intra-arterial chemotherapy were available to our patients at that time. A dedicated genetic counselling service was also not accessible to patients.

Discussion
We have presented a freestanding cancer centre’s data over a significantly long period of time in Pakistan. There is a substantial amount of illiteracy, unfamiliarity and lack of awareness to seek treatment for paediatric cancers in our setting. Some of the families that do sense a problem resort to alternative medicine before realizing the need to pursue oncologic care. There is no sex predilection in retinoblastoma, yet we see a male predominance. The patriarchal society that exists in our set-up can be a reason for this observation [8].
In the developed world patients present at an early age with a multi-disciplinary approach formulated at the onset of therapy. This results in remarkable survival outcome along with vision preservation and reduction in enucleation rates. Treatment compliance and follow-up is also better with early presentation of disease.

Follow-up of our patients was inadequate with very high rates of treatment abandonment. This is partly because of resource limited setting and potential lifesaving yet surgically disfiguring options put forward in cases of extra-ocular disease.

One of the other key issues this study highlights is the diagnosis and treatment of paediatric patients with retinoblastoma. The age at presentation is significantly more when compared to western data [8, 9, 10] subsequently resulting in more advanced disease at the time of presentation with mostly Group C to E eyes. When there is such progressive disease the primary objective is to save the patient’s life. Therapeutic options for globe and vision salvage sans enucleation or exenteration are very few [11, 12].

There are institutions in the developed world such as the Childhood Eye Cancer Trust (CHECT) and others that promote the use of smartphones in detecting a red reflex or the presence of a white reflex. The white reflex can be a sign of something more serious such as retinoblastoma. Nowadays there are smartphone applications that help parents and families detect a white reflex. These applications enable parents detect a white reflex by clicking pictures of their children.

Review of our institutional experience has led us to ascertain our practice limitations and consequently suggest areas of improvement. Firstly we need to educate families about the signs and symptoms of retinoblastoma. With the widespread availability of smartphones there is a need to educate masses about the use of these devices for detection of a white reflex. The understanding to seek cure when children have low risk disease will result in better rates of ocular salvage and sight preservation [13]. As per the International Intraocular Retinoblastoma Classification (IICR) Group A to C eyes are considered amenable to early intervention. Primary care providers at the district level in our set-up should also be trained to recognize such oncologic cases earlier and initiate timely referrals. Parents of newborns should be advised to get routine eye check-ups from primary healthcare providers.

The second tier of struggle for patients was a gap in diagnostic skills and treatment consensus between medical care providers and their respective facilities. With the development of our freestanding cancer hospital we have implemented a uniform staging work-up including pathology review and standard treatment guidelines. We recommend organizing workshops and teaching conferences to help train physicians from other institutions who are not familiar with this paediatric diagnosis yet tend to see these patients in their practice.

Our team comprises of members from paediatric oncology, ophthalmology, pathology and radiology responsible for discussing new and existing patients with a diagnosis of retinoblastoma in a multi-disciplinary meeting. We encourage our local colleagues to reach out to skilled and highly specialized medical professionals for any queries about paediatric retinoblastoma. Our institutional agenda is to propagate early detection and attempt optimal local tumour control with focal consolidative procedures such as laser photoacoagulation, cryotherapy, and local chemotherapy. We are working to introduce intra-vitreal and intra-arterial chemotherapy where possible [14] in early disease.

References:


